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PATENT APPLICATION OF

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ENTITLED

METHOD AND APPARATUS FOR AUTOMATED  
OPERATION OF IMPACTORS

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## METHOD AND APPARATUS FOR AUTOMATED OPERATION OF IMPACTORS

### CROSS REFERENCE TO RELATED APPLICATIONS

This application refers to and claims  
5 priority on U.S. Provisional Application Serial No.  
60/266,984 filed February 7, 2001.

The present application is a continuation-  
in-part of U.S. Patent Application Serial No.  
09/679,936, filed October 5, 2000 for METHOD AND  
10 APPARATUS FOR CASCADE IMPACTOR TESTING OF INHALABLE  
DRUG THERAPIES RECOVERY FOR CHEMICAL ANALYSIS, and  
Application Serial No. 09/733,108 filed December 8,  
2000, for MIXING DEVICES FOR SAMPLE RECOVERY FROM A USP  
INDUCTION PORT ON A PRESEPARATOR, both applications are  
15 incorporated by and priority is hereby claimed to both  
applications and references in their entirety.

### BACKGROUND OF THE INVENTION

The present invention relates to a process  
for automating the operation of multiple compartment  
20 impactors and apparatus primarily for use in  
determining the size distribution of particles in an  
aerosol emitted from metered dose inhalers, dry powder  
inhalers, and nebulizers, which dispense inhalable  
therapeutic drugs. The process is an automated process  
25 in various embodiments that are designed for impactors  
that have external cups or cavities forming the  
impaction surfaces, and inlets and pre-separators for  
such impactors.

In the prior art, various types of impactors have been advanced that will classify particles according to size using cascade impaction surfaces with an aerosol flow through the impactor. The principles  
5 of particle classification impaction are well known and particle classification or cut points can be very closely controlled for classification of particles into separate size ranges.

The development of an impactor that has a  
10 plurality of removable, external cups that can be separated from the impactor assembly as a unit permits rapid classification of the particles. The assembly of a plurality of cups held in a frame or manifold are processed as a unit, which forms a batch of classified  
15 particles that can be processed as a batch to remove the samples needed to determine the active ingredients formed in the particles collected in each of the different size classifications, for determining not only the efficiency of the inhaler device that is  
20 utilized for dispensing the metered dose of the inhalant, but also for washing or cleaning the cups so that they are ready for the next cycle.

At the present time, the preparation of the samples by adding solvent, extracting a sample, and  
25 then after the sample has been transported to the vials used by the analysis instruments, generally a high performance chromatograph, the steps of cleaning the impactor components, washing them, and reassembling them is primarily manual, and slow.

SUMMARY OF THE INVENTION

The present invention relates to a process for automating or semi-automating sampling particles dispensed into a set of particle impactor cups and  
5 handling the classified particles from each impactor cup and thereafter for analysis by a chromatograph or other suitable instrument.

The present invention relates to a method of using apparatus for holding a plurality of impactor  
10 cups formed or held in a manifold or frame and received directly from an impactor, such as that shown in U.S. Patent Application 09/679,936, filed October 5, 2000. The plurality of cups are processed at the same time, rather than serially in the present invention.

15 The impactor used includes an induction port or inlet into which a metered dose of an inhalable substances injected, utilizing a dosing subsystem that is commercially available. A preseparator receives the dose of aerosol from the induction port. The  
20 preseparator has a first particle classification device which will remove large particles, for example, particles too large to be easily handled by the impactor. The impactor comprises a cover with a seal body that seals on a tray supporting a plurality of  
25 impactor cups. The cover includes passageways that provide a path for the aerosol to flow through the impactor and pass through the various stages of classification. Nozzles are provided above each of the removable cups that form impaction surfaces, so that

the proper classification occurs. The cups are supported in or on a cup manifold that supports the cup tray that holds the cups. The manifold has surfaces that seal on the seal plate by clamping force on the  
5 cup manifold toward the seal plate.

A service manifold is provided which replaces the cover and seal body and which seals on the cup manifold during adding solvent and collection of samples for analysis. The service manifold has  
10 passageways and ports for injecting known amounts of a solvent into each of the cups that is held in the cup manifold. The service manifold can be supported to permit it to be rocked about a generally longitudinal axis so that when the cups have received the desired  
15 amount of solvent, the solvent can be agitated by rocking the service manifold and the attached cup manifold for insuring that there is dissolution of the particles of interest in each of the cups. Agitation also can be achieved with a vibrator or shaker, as  
20 well.

The service manifold either includes nozzles which dip into each of the cups or has openings into which tubes or syringes can be inserted and will be used for extracting a known amount of the sample formed  
25 in each cup, after which each sample can be discharged into a vial. The way of filling vials is shown in U.S. Patent Application Serial No. 09/679,936, filed October 5, 2000, and identified above.

After the extraction of the samples from the cups in the cup manifold, the same or a different service manifold is used for adding water or other wash liquid into the cups, during which the cup manifold is  
5 agitated, if desired, for adequate cleaning of the cups. The service manifold with the cup manifold sealed on the cups then can be rotated about its longitudinal axis, on its supports, to drain the service manifold and the cup manifolds through the  
10 inlet openings for various liquids provided in the service manifold.

After the cups have been washed, and if desired dried with an airflow or a gas, and also optionally coated with a desired anti-bounce coating,  
15 the cup manifold is removed from the service manifold and replaced and sealed onto the seal body of the impactor, so that the impactor is then ready for a next cycle.

The service manifold can be used for adding  
20 the anti-bounce coating of a suitable material into the cups, so that the particles will not bounce out of the cups when impacting on the surface of the cup.

A frame can be provided for holding one or more service manifolds for different types of  
25 operations, and sequentially moving the cup manifold and service manifolds together. For example, a first service manifold can be used for adding solvents to dissolve the particles in the cups and remove samples for analysis by a chromatograph. A second service

manifold can be used as a wash and dry station for the cups. The second service manifold can be held stationary, or it can be rotating for draining as previously explained. A third service manifold can be  
5 used for coating the cups after they have been washed and, if needed, dried.

In the process, the assembly of the inlet or induction port, a preseparator, an impactor cover and seal body can be maintained in a single dosing station  
10 on a turntable or can be used with a conveyor belt that will move the cup manifold to different stations for adding solvent and extracting samples. The wash and dry station, and the coating station can be sequentially used. Thus, a highly automated system is utilized in  
15 the present method.

The preseparator is a cylindrical body that can be put onto a separate fixture for adding solvent, extracting a sample and washing, simultaneously with washing the impactor cups. The particles that have been  
20 collected in the preseparator are dissolved and the solvent solution is used as a sample for determination of the total amount of drug particles that has been injected into the induction port of the impactor.

The preseparator can be mounted in a device  
25 for rotating it about two orthogonal axes, causing all internal surfaces to become wet and rinsed or washed for full sample recovery. Then a sample is placed into a chromatograph vial and handled for analysis in the chromatograph that is desired.

The remaining solution in the preseparator is dumped into a waste container or drain, and the preseparator is washed, agitated and the wash liquid (e.g., water) is dumped to the waste container as well.

5           Additionally, the induction port or inlet can be placed into a separate wash assembly and any of the active drug particles in the induction port are also dissolved and a sample placed into a vial for chromatographic analysis. The rest of the solvent  
10 solution in the throat is dumped to waste, and a wash solution is introduced into the throat. Suitable plugs are provided so that the liquid will not be lost, and one of the plugs has a passageway or port for inserting the necessary solvent, removing a sample, and adding  
15 and removing wash liquid.

The actual apparatus utilized in the present invention can be of any desired form, and the applications which have been incorporated by reference show various forms of handling these individual  
20 components.

Thus, the service manifold, and the devices for agitating the throat and preseparator are shown only schematically.

#### BRIEF DESCRIPTION OF THE DRAWINGS

25           Figure 1 is an assembled view of an impactor apparatus used for determining distribution of particles from a metered dose or dry powder inhaler;

Figure 2 is a plan view of the impactor of Figure 1;



Figure 3 is a sectional view taken on line 3--3 in Figure 1;

Figure 4 is a sectional view taken as on line 4--4 in Figure 2 illustrating the arrangement of impactor cups used in the impactor apparatus of Figure 1;

Figure 5 is a sectional view taken on line 5--5 in Figure 3;

Figure 6 is a sectional view taken on line 6--6 in Figure 3;

Figure 7 is a plan view of an impactor cup manifold used with the impactor of Figure 1;

Figure 8 is a plan view of one form of a service manifold used with the present process;

Figure 9 is an end view of the service manifold of Figure 8;

Figure 10 is a schematic side view of a service manifold drive and support for rocking and rotating the service manifold about a longitudinal axis;

Figure 11 is a schematic end view of Figure 10;

Figure 12 is a side view of a device for supporting and holding a USP standard throat during sample recovery and washing;

Figure 12A is an end view of the device of Figure 11;

Figure 13 is a side view of a device used for recovering samples from and washing the preseparator;

Figure 14A-14K are schematic representations of a first process for automating the operation and recovery of an impactor process used with metered dose inhalers, with dry power inhalers and/or nebulizers;

Figure 15 is a further exemplary schematic representation of the components of the impactor assembly, illustrating a form of the invention that permits movement of the particle containing cups between a service manifold and the impactor device;

Figure 16 is a schematic representation of the ducting for the service manifold, which can use some of the same ducts, which illustrates the different inputs;

Figure 17 is a schematic representation of a frame that will support the cover and seal body in a fixed position, and shows a modification of use of service manifolds to include a coating station for coating the impactor surface of the cups;

Figure 18 is a schematic representation of a pivoting arm having a gripper for lifting the induction port or inlet from the preseparator, and transporting it to a location for processing, where it can be inserted into the device shown in Figure 12;

Figure 19 is a schematic representation of a side view of the device shown in Figure 18;

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Figure 26 is a schematic representation of an automated arrangement for delivery of a solvent to a typical impactor cup in the cup manifold;

Figure 27 is a schematic representation of an automated arrangement for withdrawing a sample, and flushing and drying the sample line; and

Figure 28 is a schematic view of syringes  
5 for injecting solvent into a service manifold.

DETAILED DESCRIPTION OF THE ILLUSTRATIVE EMBODIMENTS

A general form of an impactor that is handled as will be described in the present invention illustrated in Figures 1 through 7 comprises an  
10 impactor assembly 10, which has a cover 24, with an aerosol inlet induction port 14. The induction port or inlet 14 can be a standard USP type inlet tube. A pre-separator 16 is illustrated on the aerosol inlet in Figure 1. The pre-separator 16 separates out large  
15 particles.

The aerosol that is passed through the impactor 10 is an aerosol generated by an automatic dosing device or inhaler 17, or other device that may be a liquid or dry powder drug inhaler, such as those  
20 used to control asthma and similar problems. Commercially available dosing devices are used for these procedures. The amount of flow from each dose or charge is small, so the internal volume of the impactor 10 must be kept low. The flow rate through the  
25 impactor will be generated in a selected manner, for example by providing a vacuum pump such as that shown at 20 on an exhaust opening (see Figure 2) from the impactor housing 21 comprising the cover and seal plate assembly. This type of impactor is described in U.S.

Patent Application No. 09/679,936, filed October 5, 2000, the specification and drawings of which are incorporated by reference.

5 The lid or cover 24 is sufficiently thick to include flow passageways on the underside. The lid or cover 24 has an opening for the inlet pipe 14A to pass through to seal plate 30 which is fastened to the underside of the cover with removable screws 12. The cover and seal plate assembly 21 are held in a support  
10 frame and manipulated in the process of the invention. The cover 24 is clamped to a base cup manifold 25, as shown with power, automatic clamps 13, operated with pneumatic cylinders 15, if desired. Only one cylinder if needed, if one clamp 13 is mounted on a fixed  
15 support to act as a force reaction member. The cylinders 15 can be retracted so the clamps release the cups and manifold 25, for processing.

The cup manifold has a number of egg shaped or tear drop shaped impactor particle collection  
20 chambers or cups 32A-32H to be positioned under a series of nozzles carrying the flow through the impactor. These cups can be removable and held in a frame that can transport all of the cups as a unit.

As shown in Figures 3, 4, 5 and 6 seal plate  
25 30 is positioned below the cover 24 and has seals in grooves on both sides to seal cross flow passageways on the underside of the cover 24 and, on the opposite or bottom side of the seal plate 30, to seal around each of the impaction chambers or cups 32A-32H to define

sealed passageways including the cups for forming the flow path. The inlet tube 14A passes through cover 25 and the seal plate 30 and opens through an inlet opening 33 into the first impaction stage cup 32A. In  
5 Figure 3 the seal plate 30 is shown with the seals 35A-35G that seal around cross flow passageways 40A-40G in the cover. Also, the nozzles 37A-37F are shown and they are supported on the seal plate over the cups 32B-32G.

The first stage cup 32A forms an impactor  
10 surface and underlies the inlet opening 33. The top opening of the cup 32 is sealed with a seal 34A on the seal plate 30 and extends transversely of the impactor to a vertical passageway 36A (Figure 3) that opens through the seal plate 30 to a crossover passageway 40A  
15 (Figure 6) formed on the underside of the cover 24.

Figure 4 is a sectional view of the cup manifold, looking up toward the cover, as shown in Figure 1, with the cups and seal plate removed, so the interstage passages 40A-40G on the underside of the  
20 cover 24 can be seen. The cup inlets on the base frame 25 are shown in Figure 3. The seals 34A-34H follow the shape of the cup openings in frame 25 Figure 4, and as shown in dotted lines in Figure 3.

The crossover or interstage passageways 40A-  
25 40G leads to a nozzle passageway or opening in seal plate 30 (Figures 3 and 6) having nozzles 37A-37F that have openings of desired size, and a desired number are provided. The aerosols containing the particles will discharge into each stage impactor surface of the cups

32A-32H of the cup manifold 25 by flowing through the cups in sequence and then through the crossover passageways in the cover. The tear drop shaped cups have wide ends under the respective nozzles 37A-37F and  
5 narrow opposite ends. The small ends of the cups align with passageways or ports 36A-36G through the seal plate and opens the respective tear drop shaped passageway in the cover 24.

The large ends of the passageways 40A-40E  
10 overlie the respective nozzles 37A-37F, which discharge into the impactor cups 32, and the impactor cups collect the respective size particles for analysis.

The passageway 40G may open to a final stage micro orifice filter nozzle 37H in cup 32H, if desired.  
15 A fluid flow outlet opening 36H opens to a short cross passageway 40H (Figure 4) in the cover 24. The passage 40H is a short cross over passageway that opens through the cover. A suitable flow line can be coupled to the passageway 40H and to the vacuum source 20 to establish  
20 an air flow from the dosing device.

The passageways in the cover that connect between nozzles are all sealed with properly shaped O-ring seals, as shown. The impactor cups in the cup manifold are also sealed with tear drop shaped O-ring  
25 seals.

The cup manifold 25 of Figure 7 is separated from the cover and seal plate assembly during the process, and sealed against a service manifold that has seals on its bottom side to seal

around each cup. The cups are shown as part of the manifold, and, if desired, the cups can be made as individual removable cups shown as cups 32G and 32H where a lip fits into an opening of a support plate  
5 as shown by the dotted lines as disclosed in Application Serial No. 09/679,936.

In Figures 8 and 9, a service manifold 100 is shown schematically. The service manifold 100 is used for providing various functions in the operation  
10 of the present automatic process. Service manifold 100 schematically shows typical passageways and ports, and will illustrate how such passageways and ports can be used. The service manifold 100 is made to overlies the cup manifold 25 and provides a way of  
15 adding and removing fluids (liquids and gases) from the impactor cups and for passing gases over the impaction cups.

The service manifold 100, as shown, has ports, such as ports 144 for adding solvent to the  
20 cup manifold 25 and the cups 32A-32H in the cup manifold, and has ports 156 for extracting liquid samples of dissolved particles from the cups as will be more fully explained. All of the ports that are used can be connected through valves, such as valves  
25 158 shown in Figure 8. The valve 158 which can be electric (solenoid) valve controlled by a controller 97.

The ports can be connected through fittings that are in turn connect to flexible small diameter

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lines 157 that are sufficiently long so that the service manifold can be rotated about a central axis as will be shown. The lines 157 can be managed in any desired manner, but they needed to have sufficient  
5 length to permit the manifold to be rotated for draining.

The service manifold 100 can be made of Plexiglas, or other suitable material, and as shown can have a longitudinally extending passageway 44A  
10 connected to a water or wash solution source 116. The passageway 44A is zigzagged, so each opening 44C that opens from the passageway 44A to a respective cup 32A-32H in an attached cup manifold 25, overlies a portion of that cup 32. The passageway 44A can  
15 discharge liquid or gas out the end of the service manifold 100, opposite from the connection of the passageway 44A to the water source 116. A valve 44D can be used to close off the outflow so that the amount of water discharged can be regulated, and  
20 water or wash solution source 116 has a shutoff valve as well so that the passageway 44A can be isolated.

A longitudinally zigzagged drying gas passageway 45A is also formed in the service manifold 100, and has a separate opening 45B from the  
25 passageway over each of the cups in the cup manifold. The passageway 45A is connected at one end to a dry gas source 140. When washing, rinsing, or drying the cups 32A-32H automatically, water or the wash solution is introduced through passageway 44A, and

drying gas can be introduced through the passageway 45A. Zigzagging the passageways is not necessary if directly opening ports for each cups are provided.

5 The cup manifold 25 can be held in place on the service manifold 100 with automatically operable clamps, shown schematically as pivoting clamps 46 operated with air cylinders 46A and mounted on the service manifold. Valves 46B for the air cylinders 46A are controlled by the controller 97 to operate  
10 the air cylinders 46A and open and close the cup manifold clamps 46. The clamps 46 stay with the service manifold 100, and the pivoting ends clear the cup manifold 25 as the cup manifold 25 is installed. The clamps 46 can be operated to hold the cup  
15 manifold 25 sealed against service manifold 100 for the various sampling and cleaning operations in the automatic process.

These clamps 46 are shown only schematically, and can be arranged as desired. The  
20 service manifold 100 and the cup manifold 25, when held together and clamped, will be agitated by rotating the assembly about a longitudinal axis of the service manifold when a solvent is placed into the cups 25 after the particles that are being  
25 analyzed have been passed through the impactor and particles are held in the cups. The service manifold 100 and cup manifold 25 will be rotated or tilted so that the dissolved particles in the solvent can be

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sampled for providing a sample to a high performance liquid chromatograph (HPLC).

After washing the cups subsequent to sampling, the service manifold can be tilted and/or  
5 rotated for draining. The zigzagged passageways, which are shown as an example, are inclined toward the drain end or the inlet end, as desired.

In some instances, the wash liquid will be directly injected into the cups, through ports in the  
10 service manifold overlying the cups, and then the rotation of the service manifold would permit draining out through those ports.

In the process that is shown, the service manifold 100 can be held in one position, and then  
15 the cup manifold moved to mate with the service manifold in that position. Schematically shown in Figures 10 and 11 is a framework 48 that is fixed to a main support, and which has depending legs 48A and 48B that have bearings at their lower ends for  
20 supporting shafts 49A and 49B on the ends of the service manifold 100. The clamps 46 are also shown in Figure 10, and it can be seen that they are in their open position, and the cup manifold 25 has been moved up, which would be done with suitable actuators, not  
25 shown, in the direction as indicated by the arrow, and the cylinders 46A are operated to move the latch members to their dotted line position holding the cup manifold 25 tight against the seals on the service manifold 100.

The shaft 49B is rotatably driven with a stepper motor or other suitable reversible controllable motor 50 operating through a gear train or suitable drive 52 to drive the shaft 49B under  
5 control. The motor 50 can be controlled by the controller 97 as part of the program for automatic operation or the shaft 49B can be manually rotated, if desired.

As shown in dotted lines, the service  
10 manifold 100 and cup manifold 25 together (as a unit) can be rotated to approximately a 90° position, as shown in Figure 11 by dotted lines, if desired, and the controller 97 operating the motor 50 will let the operator incline the service manifold 100 and cup  
15 manifold 25 as they are held together as an assembly 101 by the clamps 46 to any desired rotational position.

Referring to Figure 12, an apparatus for automatically holding the induction port 14 in  
20 position after it has been removed from the impactor assemblies, as will be explained, used for adding a solvent for extracting a sample, and for the washing and drying operations is illustrated. The stand or frame 52 can be supported adjacent to the impactors,  
25 and when the induction port or inlet 14 is removed from the cover, the induction port can be put into stand 52 which comprises a mixing device or cradle 53.

The cradle 53 includes a block 53A which is recessed to receive the corner portion of the USP inlet with the open ends of the induction port inclined upwardly.

5           The stand 52 has a base 52A, and upright end members 52B that are spaced apart, and which support bearings 52C that rotatably mount shaft portions 53B that in turn are used for supporting the cradle 53. The cradle 53 has a base 53C, and end  
10 supports 53D fixed to the base. The upright members 53D have bent wall portions 53E that are formed at substantially a 45° angle to the main upright portions of the end support 53D. These bent wall portions 53E have openings therein that slideably  
15 receive the rod portions 54A of air cylinders 54 that are mounted on these bent portions 53E. The rod portions are shown at 54A and the rod portions can be retracted by operating the cylinders 54, or can be moved to the positions shown in solid lines, to  
20 engage the end portions covering the openings of the legs 14B and 14C of the induction port 14.

          The rods 54A support cup like cap members 54B that have suitable seals for sealing on the edges of the openings of the legs 14B and 14C, and also can  
25 have fittings 55 that pass through ports, to permit using the caps for injecting solvent material and letting liquid material drain. The fittings 55 can be provided at either one, or both, of the caps 54B.

When the air cylinders 54 are extended, by operating valves 56 that operate the respective air cylinder 54, under control of the controller 97, the caps 54B will be sealed against the open ends of the induction port 14, so that the interior induction port passageways are sealed. Suitable solvents for the particles on walls of the interior walls of the induction port can be added into the interior by operating charge valves through the connections 55.

10 The connections 55 are connected to flexible lines so that the cradle 53 can be moved about the axis of the shafts 53B by operating a motor 57, which again is controlled by the controller 97. The motor 57 can be a stepper motor or other reversible motor. Pneumatic

15 motors also can be utilized, if desired.

The cradle 53 can be moved so that the induction port 14 can be rotated up  $180^\circ$  around, if needed, and the solvent that is retained inside the tubular inlet will flow back and forth as the inlet is rocked or agitated, and the solvent will contact

20 all the interior surfaces of the tubular sections to insure that any particles that are left in the inlet tube are accounted for by dissolving the particles in the solvent.

25 By tilting the cradle 53 so that the connections 55 in the cups 54B (and the open ends of the inlet 14) are extending downwardly, and draining liquid from both ends through connections 55, a sample can be obtained for an analysis which can be

Figure 13 shows an arrangement for dissolving particles in and removing samples from and washing the preseparator 16. The outer configuration of the preseparator is differently shaped from that shown schematically in Figure 1. The preseparator is used for classifying large particles, and thus it is necessary to extract a sample of particle content from the preseparator as well. The preseparator 16 is formed with an outer wall 16A that defines an interior chamber 16B, and there is a dividing wall 16C that acts as an impactor plate for material coming in through the inlet line or pipe 16D.

The fixture for handling the preseparator for sample extraction of the present invention includes a frame 69 that has a base 69A supporting upright members 70A and 70B, that in turn rotatably mount a cradle 72. The cradle 72 has shafts 74A and 74B that are rotatably mounted on suitable bearings on the upright members 70A and 70B of the frame 69. The cradle 72 has a lower cross support member 76 and an upper cross support member 76A joining the side

members 72A and 72B. The lower cross member 76 supports a cup 80 that will receive the end of the outlet pipe 14A and form a seal on it. The cup 80 is supported on a cross member 76 and has a shaft 80B  
5 that rotates in a bearing in the cross member 76. A turnstile drive member 82 is mounted on the shaft 80B, and has a plurality of arms, four as shown, that protrude out from the center of the turnstile at 90° intervals and will engage an upright drive 82E. The  
10 arms are shown at 82A, and 82B and 82C. The fourth arm protrudes outwardly from the turnstile in an opposite direction from the arm 82A.

The cup 80 will freely rotate, if desired. Post 82E fixed to the base 69A acts as an actuator  
15 for the turnstile, so that when the cradle 72 is moved past so the arms go past the post 82E so the arms engage past the post, the preseparator will rotate a quarter of a turn about the axis of shaft 80B. This occurs each time the turnstile drive  
20 member moves past the post 82E.

The upper cross member 76A supports a short air cylinder 86 that has a rod 86A that in turn supports a cup 86B. The rod 86A can be extended toward and retracted from the inlet tube or pipe 16D,  
25 or move down in a sealing arrangement with the pipe 16D when the preseparator 16 is held in position with a suitable robot arm handler or the like. The pneumatic cylinder 86 can be operated through a valve 86C that is controlled by the controller 97. Cap 86B

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also has a fitting, 86E that can be connected to  
suitable flexible hoses for injecting solvent, and  
also there can be a second or third fitting that  
passes through the cap 86B to carry in wash water,  
5 and also to form a drain when the unit is inverted.  
A mechanical threaded rod can be used in place of the  
actuator 86.

10 The lines connect to the fittings on the  
cap 86B must be sufficiently loose or slack so that  
the preseparator can be inverted in one direction of  
rotation, at least, or wireless controls also can be  
used. The cradle 72 can be rotated about the axis of  
the shafts 74A and 74B with a motor 81 controlled by  
the controller 97 in a normal manner for operating  
15 the motor to rock the preseparator, for agitating the  
solvent, and for positioning the preseparator 16 in  
the proper position for draining, capturing samples,  
and the like.

20 The devices shown in Figures 12 and 13 are  
more fully described in co-pending United States  
Application 09/733,108 filed December 8, 2000, which  
is incorporated herein by reference.

25 The general process of the present invention  
is illustrated in Figure 14A-14K, and includes the  
impactor assembly indicated at 10, which has the  
induction port 14, a preseparator 16, the cover 24 for  
the impactor that has the ducts and passageways that  
lead to various cups, which are mounted on a seal body  
30. The cups may be supported in a separable frame

that can be in turn supported to form an underlying cup manifold 25. The seal body 30 carries seals for sealing around the edges of the cups. It is to be understood that the devices that are shown in the process are schematically shown, but that the cup manifold can have the number of cups shown in Figures 1-7, and the agitating-moving devices can be also as described in Figures 8-12.

A dosing device 17 of standard form, such as those now commercially available provides a metered dose of a drug material into the induction port 14, such as a dry power, liquid, or some nebulized components. Additionally, a first service manifold shown at 100 is provided in the system for fitting to the cup manifold 25 and providing connections to the various liquids and gases that are used in the overall automated process for recovery of samples, from the impactor cups and for cleaning the impactor cups 32 and other components.

After an inhaler or dosing device has discharged into the induction port 14, the automation process generally follows a process whereby the impactor components are separated, and the cup manifold 25 containing the impacting surfaces holding the classified particles is then transferred to a station where solvent is added to the cups for dissolving the drug particles of interest. A sample is recovered, and the sample is then transferred to a high performance liquid chromatograph (HPLC) or other instrument for

analysis. After this is done, the solvent is drained, in a suitable manner, and the cups 32 are washed and dried. Optionally, an anti-bounce coating solution is added to the cups to provide a coating on the impactor surface that will tend to make particles classified into the cups adhere in place and not bounce out. After this process, the impactor is ready to be reassembled by clamping the cups manifold 25 to the cover and seal body of the impactor.

While the cup manifold 25 is being handled and processed for recovery of samples and for washing and drying, the induction port 14 and the preseparator 16 that are used will be removed from the impactor device cover and seal body assembly 21 and will be transferred to suitable automated stations such as cradle 53 and frame 76 for sample recovery and washing in sequence. Then the induction port 14 and preseparator 16 can be reassembled onto the cover.

Referring to Figures 14A-14K, which together provide a schematic flow diagram of the automated system in the first form of the invention, the showing includes a series of process steps, separated out as the Figures 14A-14K for automated handling of the dosing, sampling, and cleaning related to the impactor device of the present invention.

As shown in Figure 14A, the impactor 10 is assembled, and receives a dose of an inhalant from a dosing device 20, such as a dry powder in a carrier of air, through the induction port 14, and into the

preseparator 16, where large particles in the dose are separated out. The preseparator 16 is connected to the inlet of the seal body 30 of the cover and seal body assembly 21, called an impactor assembly through the cover, and the particle impaction takes place to separate out particles as to size into a plurality of cups 32 (specifically 32A-32H), as previously explained. The cups are either formed or removably held in a cup manifold 25.

10           The cup manifold 25 is to be understood as having a plurality of cups 32, each with particles or droplets in the cup classified as to size after passing through the impactor. In the next step of Figure 14B, the impactor cover 24 and seal body 30 assembly 21, which can be held stationary, is supported in place, and the cup manifold 25 is removed from the impactor assembly 21. This can be done by releasing clamps 13 and lowering the cup manifold 25 from the cover 24 and seal body 30 with an actuator shown schematically at 101A.

25           The cover 24 and seal plate 30 are supported in a selected manner or can be lifted with a robot arm after the clamps are released. Additionally, the inlet throat 14 and preseparator 16 are removed from the cover 24, and transported to the preseparator and throat sample recovery/wash station shown in Figures 12 and 13, using a robot or turret for each part as shown in Figures 18-21. Any particles of the dose material that may be clinging to the wall of the induction port

14 will be dissolved in a solution and analyzed, and the material separated out by the preseparator 16 also will be subjected to a solvent treatment for recovery, and then the preseparator 16 and induction port 14 will  
5 be washed as described in connection with Figures 12 and 13.

It should be noted that the service manifold 100 is maintained in a desired position, and the cup manifold 25 is then shifted into position under a  
10 service manifold with an actuator 101 as shown in dotted lines in Figure 14B and in solid lines in Figure 14C. The cup manifold 25 can be raised automatically once it is in position under the service manifold with an actuator (or elevator) 101A or 102 to bring the  
15 edges of the cups 32 in the cup manifold 25 up to seal against the service manifold 100, as shown in Figure 14D.

The cup manifold 25 is then in position in Figure 14D to receive a solvent from a solvent source  
20 104. The solvent can be provided through a valve 106, and through a metering loop, as shown in Figure 26, so that a desired amount of solvent is injected into each of the cups 32 in the cup manifold 25. The solvent can be sequentially added to each cup 32A-32H, or can be  
25 simultaneously introduced into each of the cups by operation of individual valves 106 and associated metering loops for each of the cups, and operated automatically by controller 97.

Once the solvent has been introduced, the service manifold 100 is moved to a rack such as bracket 48 and mounted on pivot shafts 49B and is rocked, as shown in the process step Figure 14E. The support is the mounting frame 48 and drive as previously shown and explained in Figures 10 and 11, including the motor 50, to rock the service manifold and cup manifold 20. The solvent illustrated at 108 in each of the cups 32 in the cup manifold 25, is this agitated to insure that the classified particles from the injected dose are dissolved and formed into solution that can be analyzed in a chromatograph.

In Figure 14F, the service manifold 100 is connected to a sample recovery loop 112 shown in more detail in Figure 26, that will be automatically operated from controller 97 to transfer the desired amount of a sample containing the dissolved particles from each of the impactor cups to a chromatograph vial indicated at 113. The cup manifold 25 and service manifold 100 are inclined approximately  $90^\circ$  in the frame 48 to do this, so that the solvent in each of the cups drains to a particular side or end of each cup for extraction of a sample for analysis.

After the desired sample is extracted, the remaining solvent solution can be drained to waste by rotating the service manifold and cup manifold unit for draining, as also shown in Figure 16. As illustrated in Figure 14G, wash water can then be added from a source 116, through the service manifold 100 into the cups in

cup manifold 25. The inversion of the cup manifold 25 is shown in Figure 14H so that the liquid material can be permitted to drain out in a desired manner. The wash steps of Figures 14G and 14H can be repeated and a  
5 rinse cycle can also be repeated to insure that the cups 32 are adequately cleaned for the next process.

The cover and seal plate also can be filled with solvent and rocked and then washed as well.

When the wash, and any desired rinse is  
10 done, and also, after a drying gas, which can be heated, has been used, if desired, to dry out the impaction cups 32, the cup manifold 25 is separated from the service manifold 100 by operating the latches 46 with the controller 97, and lowered with elevator  
15 102 as shown in Figure 14I. The cup manifold 25 is then shifted through a suitable actuator 101 or other member to a position underlying the cover 24 and seal body 30 in the impactor assembly 21, and then the cup manifold 25 is raised with actuator 101A to again seal  
20 onto the cover and seal body assembly 21 and held with automatic clamps 13, operated by air cylinders 15 and controlled by controller 97. The impactor assembly 21 is again ready for operation as shown in Figure 14K. The impactor and seal body 21 is shown in Figures 14A-  
25 14K, since it remains adjacent the service manifold 100 as the service manifold and cup manifold are put through the process.

Subsequent to the washing, if desired, the cup manifold 25 can be coupled to a separate service

manifold, for coating with a suitable coating that would reduce the amount of bouncing of particles.

After the fully automatic operation for recovering samples from the impaction cups 32 of the impactor 10 shown in Figures 1-7, the cleaning or washing, the drying and the return of the cup manifold 25, the preseparator 16 and induction 14 to the cover and seal body assembly 21, the impactor 10 is ready for another cycle.

Figure 15 is a schematic representation of a typical frame that is used for carrying out the process of shifting the cup manifold 25 to the service manifold for carryout the various process steps disclosed in Figures 14A-14K. A frame 126 comprises a table that supports the cover and seal assembly 21 on a suitable bracket 128, on an upright support 130. The service manifold 100 is supported on the bracket 48 as shown in Figures 10 and 11 so that it can be rotated about a central axis on shafts 49B. The service manifold 100 is rocked and rotated with the motor 50. An arm bracket 129 for holding bracket 48 is shown schematically. The frame 126 forms a tabletop with movable sections 120 and 121 that are elevator or lift sections operated with the actuators 101A and 102.

The cup manifold 25 is shown in registry with the service manifold 100 in Figure 15, and an elevator section 121 supporting the cup manifold 25 is supported on the actuator 102. Upon raising of the cup manifold 25, a seal is made between the service



manifold 100 and the edges of the cups 32A-32H and the manifold 25 and 100 can be automatically joined together with clamps 46 and then the actuator 102 retracted, all under control of controller 97, or by  
5 operator control of switches. A lateral actuator 101 is supported on a frame post 130 is used for moving the cup manifold 25 laterally from the assembly into registry with the service manifold 100 when desired. An automatic coupler can be used between the cup  
10 manifold 25 and the rod end of the actuator 101 rod. The rod can merely push the manifold over to the service manifold, but needs to be coupled for return.

The supports 129 and 48 permit the service manifold 100 to rotate 180° if desired, and also rock  
15 back and forth for agitation of the solvent, as well as for the wash and rinse cycles. These portions are illustrated in Figure 16.

The preseparator 16 and the throat are illustrated, but these are moved to their own solvent  
20 recovery and cleaning station for processing.

While the cover and seal body assembly 21 is held as an assembly in a stationary position on the frame 126 for all of the process steps described in Figures 14A-14K, after a fixed number of sampling  
25 cycles, which is determined by the operator, the cover/seal body (impactor) assembly 21 will be removed from its support for cleaning and a new impactor body assembly can be inserted in place.

The old impactor assembly 21 will be cleaned at a remote location, or off line. The impactor assembly 21 can be held in a slide frame and removed in a direction transverse to the movement of the cup manifold 25. This movement can either be done by an operator or mechanically with a turret, robots, or air cylinders as part of the automated system. A magazine of clean impactor assemblies 21 can be held on one side of the bracket 128 and a magazine for the dirty or used impactor assemblies can be on the other side of the bracket 128. Again, the impactor assembly 21 is not cleaned after each impaction or dosing cycle, because the flow through the seal body generally keeps the passages free of particles.

The service manifold 100 remains in bracket 48 as shown in Figure 16 for all of the process steps of Figures 14A-14K. The cup manifold 25 has two degrees of motion in Figures 14A-14K. It goes up and down on the elevator sections 120 and 121 using suitable actuators 101A and 102, which are schematically shown as a way of providing the motion, and moves to the left or right along the support table with actuator 101. The actuator 101 shown for left/right sliding motion also could be replaced with a chain conveyor or similar transporting device. The up and down elevator motion of the actuators 101A and 102 are used to clamp the cup manifold 25 to the cover/seal body assembly 21 or to the service manifold 100. In the case of the stationary cover and seal assembly 21,

the actuator 101A may be used to hold the cup manifold 25 in a sealed position operable for the impaction process without clamping. Manually moving and attaching the cup manifold 25 to the impactor assembly 21 also  
5 can be done without undue operator time.

The actuator 102 can hold the impactor assembly up against the service manifold 100 for adding solvent and sampling, but when the service manifold is to be agitated or rotated, a suitable automatic  
10 clamping assembly such as clamp 46 is used for holding the cup manifold 25 against the service manifold 100 so the two manifolds move as a unit.

Devices such as air cylinders, as shown, racks and pinions, or stepper motors can be used for  
15 providing these necessary motions.

Figure 16 is a schematic representation of a service manifold 100D having a dome over each cup or it can be over an entire cup manifold, but each cup must be individually treated for adding solvent and  
20 sampling. Connections that can be made directly through the manifold 100D for injecting liquids into and draining from the cups 32 in the cup manifold 25. The service manifold 100D can have fittings that connect through ducts in the service manifold, either  
25 with separate connections and separate ducts, or multiple connections to one duct. The service manifold 100D provides solvent from the source 104, wash water from the source 116, dry air for drying the cups in the cup manifold 25 from a source 140, and a coating

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material from a source 142. All of these can be operated through the automatic valves such as valve 106 that connect separate lines to passageways shown at 144 in the service manifold. A waste drain to a waste outlet 143 is also provided.

The valve arrangements will be described in connection with Figures 26 and 27. In Figure 26 the arrangement for pre-measuring the solvent injected is shown.

10 In Figure 26, the valve 106, is shown as having two components namely rotary valves 106V and 109. The rotary element of valve 106 is connected at port 106A to the pressurized solvent source 104. A fixed volume sample loop line 107 connects to second  
15 valve portion 109. Valve portion 109 is connected to waste or drain 143 in the solid line position. When controller 97 is caused to move valves 106V and 109 to this solid line position, the loop line 107 fills with solvent. When the valves 106V and 109 are shifted to  
20 their dotted line position, as shown in dotted line at 109B shifts to connect a source of air under pressure 111 and this pressure causes the solvent in lines 107 to be discharged through the passage in valve 106V to position shown in dotted lines at 106P to the service  
25 manifold ports and then to the cups in the cup manifold 25. This arrangement permits automatic operation of the solvent addition to the cups 32. A separate valve arrangement 106V can be used for each cup.

In Figure 27 a valve arrangement for withdrawing a sample from each cup is shown. A valve 146V has a portion 146 that in its solid line position has a port 146A and its associated passageway connected to a vacuum source for waste 147. The common port 146B is connected to a 1 ml line sample loop 112, which is connected to a common port 147A of a valve portion 147. A port 147B is connected to a dip tube 156 (see Figure 16 as well) in a cup 32 in the cup manifold 25. This is done with the service manifold 100D rotated between 0° and 90° as shown in dotted lines at 100X in Figure 16. The desired volume (1 ml.) is captured in loop 112, and then the valve portion 146 and 147 are shifted move the internal passageways to their dotted positions. Nitrogen enriched air under pressure from the source 111, which is connected to port 146C of valve portion 146 forces the sample out of loop 112 through valve port 147C out into a vial 113 for the high performance liquid chromatograph.

The vial 113 is moved with a robot arm shown in Figure 22, or with a standard handler such as that sold by Gilson Inc. of Middleton, Wisconsin. Automatic three axis handlers are commercially available and are shown in US-A-6,143,573, incorporated by reference, issued November 7, 2000.

The sample loop 112 can be flushed by connecting port 147C to a waste connection and leaving valve portion 146 with port 146C connected to its

internal passageway shown in dotted lines to purge the loop 112 with nitrogen enriched air from a source 111.

A separate dip tube 156 can be provided for each of the cups 32A-32H, and connected through valves  
5 similar to those shown schematically for drawing out a sample volume set by loop 112.

The dip tube 156 can also be connected directly to a syringe that will draw out the sample after the solvent has been agitated sufficiently to  
10 dissolve the particles in the cups, and then the syringe can be operated to directly deposit the sample into a vial 113. For flushing, water can be injected with a suitable valve and draining can be done by inverting the service manifold 100 or 100D to its  
15 position shown in dotted lines at 100Z in Figure 16.

Referring specifically to Figure 17, a simplified schematic of the use of three separate service manifolds, 100-1, 100-2, and 100-3, is illustrated. In this form, a frame 151 is made to  
20 support the impactor assembly 10, which is shown separated in this Figure with the induction port or inlet 14, the preseparator 16, and the impactor assembly 21 illustrated and separated. The induction port 14 is being held on the robot turret described in  
25 the following Figures 18 and 19, and the preseparator is being held on the robot turret described in the following Figures 20 and 21. The robot arms can be of selected design and many are known.

The cup manifold 25, is shown separated from the cover and seal body or impactor assembly 21, and it is shiftable by an actuator 101. The distance across the frame 151 is greater than shown before, so the  
5 actuator can be used in stages, or can be a long actuator that will move the manifold 25 all the way across the frame 151.

The elevators that have been shown can be used again, with the actuator 102 used for raising and  
10 lowering the cup manifold 25 relative to the first service manifold 100-1 where the dissolution of particles in an injected solvent and a sample for the liquid chromatograph would be obtained. In this station, the service manifold would be rocked as  
15 previously explained.

After the sample is obtained the cup manifold 25 is moved to the service manifold 100-2. An elevator 102A can be used for raising and lowering the cup manifold 25 after it is shifted into alignment, and  
20 mating it with the service manifold 100-2 which is the wash and dry station. In this instance, a service manifold configuration similar to that shown in Figures 8 and 9 can be utilized for the wash and dry operation.

An elevator 102B can be used for raising the  
25 cup manifold 25 up to seal on the service manifold 100-3, where the cups 32 can be coated with a suitable coating material before the cup manifold 25 is placed back onto the cover and seal body assembly 21.

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A single service manifold does not have to serve all of the functions, but a frame that has several service manifolds operated automatically in sequence can be used. The controller 97 can be used, and sensors that indicate the ends of cycles can provide signals to the controller, or a timer 99T can be used for each operation, as shown at 99A, 99B and 99C in Figure 15.

The controller 97 operates the elevators 102, 102A and 102B and a suitable lateral shifting device such as that shown as actuator 101. Separate devices could be used between each of the service manifolds, or a conveyor chain can be used for moving the cup manifold 25 laterally across the frame 151 once it is separated from the cover and seal body assembly 21.

Figure 18 is a top plan view of a typical turret or robot arm 170 that can be used for handling the induction port of inlet 14, for recovery of particles that may have been clinging to the wall of the induction port 14 and also for cleaning.

As shown, the turret or robot arm indicated at 170 may be any desired form. It is mounted on a suitable support 172 on a frame that is adjacent to or on the same frame as that shown in Figure 15 in one form of the invention, shown in additional forms of the invention. The turret or robot arm includes a column 174 (Figure 19), and a laterally extending arm 176. The column 174 is made so that the arm 176 can be



raised and lowered vertically along the column 174 using a suitable drive indicated at 178 this can be a motor or actuator. The arm 176 also is mounted for rotation about the column 174 with a suitable ring gear or other type of drive 180. A gripper 182 is provided at the outer end of the arm 176, and this gripper can be pneumatically actuated or otherwise actuated to open, and then close to grip around the cylindrical, vertical section of the induction port 14. Because the cover/seal body assembly 21 is secured in place, the gripper 182 can grip the induction port 14, and then the actuator or drive 178 can be operated to lift the arm 176 and remove the induction port from the preseparator 16. The preseparator can be gripped with its own turret or robot arm, as will be explained, so that the separation of the parts occurs at the right place.

The drive 180 then can be operated to rotate the arm 176 and induction port 14 to position it in a bracket or fixture, as previously shown in Figure 12, for sample recovery by injection of a solvent, and subsequent washing and draining. The valves shown in Figures 26 and 27 can be used for the operations solvent injection, sample recovery and wash as described in connection with Figure 12.

Figures 20 and 21 show a separate turret or robot arm 190 is illustrated for handling the preseparator assembly 16. Again, because the cover and seal body assembly 21 is secured in place, the

preseparator 16 can be removed from the cover and seal body assembly 21 by a vertical motion. In this case, the turret or robot arm assembly 190 that is identical in construction to the arm described in Figures 18 and 5 19 is provided with a gripper 192 that is of size to grip the preseparator 16, and can be automatically operated to open and close to grip the preseparator.

Then, the actuator or drive 178 on the post or support 191 for the passing and lowering the turret or robot arm 190 can be operated to lift the preseparator 16 up, and the drive 180 can rotate the lateral arm 193 of the robot arm assembly 190 to a desired position where the preseparator will be placed into a fixture for adding solvent, and to provide a 15 sample of any particles that may be impacted or classified in the preseparator 16. This sample is drawn out and transferred to a vial for a chromatograph for analysis and forms part of the overall sample being recovered. The preseparator 16 then can be washed, 20 rinsed and dried in the fixture shown in Figure 13. The injecting solvent and sampling operations could be done with the valves shown in Figures 26 and 27.

It should be noted that in both the operations for the preseparator 16 and the inlet 14, 25 the grips can have wrist actions so that they can be rotated about at least two axes, to accomplish the rocking or agitation that is necessary for insuring that the solvent dissolves the particles, and that the unit is adequately washed. This would then eliminate

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the need for separate fixtures for rocking or agitating the cup manifold and solvent.

Multiple axis operation of grippers is well known in the field and many automatic vial handlers use grippers that rotate.

As shown in Figure 15 a central controller 97 can be used for controlling all of the operations through a suitable program represented at 99. The program can control the operations of the various movements of the cup manifold, the rotation of the service manifold, and other operations including the wash operations, drying operations, and the solvent recovery operations so that sequentially the actions will take place as programmed in from the program 99. All of the valves, cylinders, and motors, including those of the turret arms that have been described can be controlled from the controller 97. Sensors can be utilized, as shown, for determining ends of cycles or timers 99T can be utilized for timing the operations for washing and the like.

In Figure 22, a plan view of a typical full robot arm assembly that can be used with the present invention using a turntable 165 is illustrated. The robot arm 160 is a 3-axis robot arm that has an elbow joint 160A, and a gripper end 160B. Cup manifold 25 is shown in one spot, and the cover and seal plate assembly 21 is also shown adjacent the cup manifold 25. The robot arm can pick up individual cups, if they are removable or can do sampling, with the cup manifold 25

at the position shown. A further vial handler robot arm 163 is positioned on an opposite side of a turntable 165 from the robot arm 160, and it can pick up vials that are held on the turntable 165, or vials  
5 that have been filled, and put them into a storage container 167, as shown,

Various work stations 169A, 169B, and 169C can be provided as needed for operation of the overall automated system of recovering samples and transferring  
10 them to a manifold or magazine for a chromatograph.

In Figures 23 and 24, a turntable indicated at 200 is represented as a form of the invention in which the operational devices can be positioned relative to the turntable, in particular the service  
15 manifolds. A plurality of service manifolds can be used, one for each of a selected number of operations.

The turntable 200 is mounted onto a support at a desired height (Figure 24), and as shown the table member 202 is supported on a center shaft 204 that is  
20 driven through a power drive 206. The table 202 rotates in the direction as indicated by the arrow 208 in Figure 23, from the base station where particle dosing and impaction takes place, indicated generally at 210A. After the dosing device 17 is operated, the  
25 cup manifold is movable to a plurality of additional stations, using service manifolds. In the station 210A, the automatic dosing device 17 is provided for charging the inlet or induction port 14, and then the impactor that has the passageways for causing the fluid

or aerosol introduced by the dosing device 17 to pass through various classification stages and nozzles to impact particles onto cups 32 in the underlying cup manifold 25.

5                In this form of the invention, the turntable as shown has four stations, and each of the stations has an underlying elevator platform 212A, 212B, 212C and 212D. Each of these elevator platforms is supported on a suitable actuator or operator 214, so  
10                that it can be raised up from the plane of the table 202 to support the cup manifold 25 that it underlies. The actuators 214 can be air cylinders or screw actuators.

                 In the form shown in Figures 23 and 24 at  
15                station 210A, the elevator platform 212A would be raised to support the cup manifold 25 held on cover and seal plate after the impaction has taken place, and after release of clamps such as clamp 13, the cup manifold 25 is lowered.

20                It should be noted that the cover and seal plate or compactor assembly 21 in Figure 23 is mounted in a fixed frame 217 that has side members that come up along the sides of the compactor assembly 21 to support it in place. A vertical post support 219 that supports  
25                frame 217 is supported to the exterior of the indexing table 202, so it is out of the way.

                 The turntable 200 can be indexed to any one of four different positions, using the drive 206 in a normal manner with a controller, and when the cup

manifold 25, which has been lowered by elevator 212A is rotated to the position 210B, it is underlying a service manifold 100B, that is connected to sources of solvent 104, so that suitable solvent can be injected  
5 as shown in Figure 26, and in this station the service manifold 102B is mounted onto the frame 48, that will permit rotating or rocking the service manifold 100B about a generally horizontal axis that extends longitudinally of the service manifold. The frame 48  
10 can be supported on an upright 220 similarly to the mounting frame 129 in Figure 15, and driven by motor 50 so that it can be rocked or moved back and forth about the horizontal axis to agitate or oscillate the solvent, to form a solution of the particles that are  
15 being analyzed.

Once the solution has been adequately agitated, so that the liquid containing dissolved particles can be sampled, a sampling device indicated generally at 224 and as shown in Figure 27 is connected  
20 to the service manifold 100B to extract the samples from each of the cups 32, and transfer to vials 113 for the chromatograph, in the form generally as shown in figure 27.

The elevator platform 212B is then raised  
25 back up, to support the cup manifold 25, the cup manifold is released from the service manifold 100B (it would have been clamped in place with clamps 46) and the table 202 is indexed to the station 210C where a second service manifold 100C is positioned in a frame,

which can be a fixed frame so the service manifold is held stationary. A frame 48 for rotatably mounting the manifold 100C about a horizontal, longitudinally extending axis is shown for illustrative purposes. The shafts that mount the service manifold 100C can be driven with the motor 50. The cup manifold 25 may be held with clamps 46 as previously shown. The elevator platform 212C is raised to position the underlying cup manifold 25 up against the service manifold 100C, and suitable wash water from a source 116 is provided.

This is shown schematically, but each of the cups would be washed. When done, the clamps 46 would be released, elevator platform 212C would be lowered, after the cup manifold 25 is clamped onto the service manifold 100C. The service manifold 100C can be oscillated around its longitudinal axis. The connections to the wash water source 116 would be flexible so that the service manifold 100C could be inverted for draining after the wash had been completed as shown in Figure 16. Two or more washes can be carried out, as well as a rinse cycle. The water source 116 could be something other than plain water, if desired. The wash cycle also can take place at service manifold 100B.

At station 210C a suitable dry gas can be introduced to the interior of the cups in the cup manifold for drying the cups. This can merely be air or some other dry gas from the source 140.

When the cup manifold 25 under the service manifold 100C is being serviced, a second cup manifold is provided to the service manifold 102B and the second cup manifold then can be provided with the solvent for  
5 dissolving the particles, and providing a sample to the chromatograph.

After the cup manifold under the service manifold 100C has been dried, the elevator platform 212C would be raised, the cup manifold 25 would be  
10 released, and the elevator platform 212C would be lowered. The table 202 would then again be indexed, and at the same time the cup manifolds under the stations 210A and 210B can be supported on the respective elevator platforms and the table 202 then  
15 indexed one place to bring the initial cup manifold underneath the coating service manifold shown at 100D, at station 210D. The service manifold 100D is provided to a source of coating material as is well known, and which is indicated at 142. The actuator for the  
20 elevator platform would travel with the turntable.

The coating process involves applying a liquid containing a coating material in a solvent in each of the cups, and letting the solvent carrying the coating material evaporate. This drying also can be  
25 done by providing a source of dry air to the manifold in station 210D as well. Service manifold 100D is used after the elevator 212D had been raised to hold the cup manifold 25 against the service manifold 100D. The service manifold 100D is held in a fixed frame 230 and

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clears the turntable. The manifold 100C also can be in a fixed frame as the wash is done at service manifold 100B.

5 The turntable can be indexed one cup manifold at a time, depending on how quickly the induction port 14, and the preseparator 16 can be subjected to solvents, samples removed, and then cleaned. If this occurs rapidly, the number of cup manifolds that can be placed under the impactor  
10 assembly 21 at the station 210A can be increased so that there would be more than one cup manifold being processed on the turntable at a time. However, even with a complete indexing, the robot arms that are shown schematically in Figures 18-21 can be used for handling  
15 the throat 14 and the preseparator 16 as described to recover the needed samples and wash and dry the induction port and preseparator.

Figure 25 shows a still further modified form of the invention, which is shown only  
20 schematically, and in this instance, a cover and seal plate or impactor assembly 21 is shown mounted onto a frame 250A that can be vertically moved, relative to a conveyor belt 252. The conveyor belt 252 is mounted on suitable pulleys or drums 254 and 256, and the pulleys  
25 or drums can be driven with a motor 258. The conveyor belt 252 is supported on suitable supports so that it does not deflect substantially, and it supports a plurality of cup manifolds 25A-25H that are fixed to the conveyor and which are sequentially used. The

conveyor belt 252 can be intermittently operated, or in other words can move between the individual stations that are illustrated, and stopped as much as desired or as long as desired in each of the stations.

5           The frame 250A is capable of being raised and lowered, so that the cover and seal plate assembly 21 can be moved to mate with and seal on the individual cup manifold shown at 25A, for impaction from a dosing device 20 through the induction port 14, and the  
10       preseparator 16, as previously explained, at an impaction station 248A.

          After the impaction of the dose from the dosing device 17, the conveyor belt 252 is moved by operating the motor 258 to a second station 248B, where  
15       a service manifold 100E is positioned on a vertically movable frame 250B.

          The service manifold 100E is one where the solvent for dissolution of the particles is provided from a solvent source 104, and when the frame 250B  
20       lowers the manifold 100E onto a cup manifold 25B, the solvent is injected into each of the cups as explained, using the metering valves of Figure 26. In this instance, other types of agitation of the solvent can be used such as an air agitator that would be part of  
25       the station 248B and would be provided through the same passageways as the solvent from source 104. Additionally, a vibrator, such as an ultrasonic vibrator indicated at 264 can be used on or in the

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service manifolds or cup manifolds for vibrating them to agitate the solvent adequately.

After the solvent has been agitated, the conveyor belt 252 can be indexed to station 248C where the sampling device such as a syringe indicated at 114 is connected to a manifold 100F. The manifold 100F is also operated with a vertically movable frame 250C to permit it to seal on a cup manifold 25C, so that a liquid or gas sample can be removed and sent to a vial for a chromatograph suitable analyzing instrument, again using the valves and lines previously shown.

The frame 250C is used for moving the service manifold 100F down against the edges of the cup manifold 25C for sealing before the sample is  
15 retrieved.

When the sample has been retrieved from each of the cups 32 in the cup manifold, the conveyor belt 252 is indexed again, and it is in station 248D that the cup manifolds shown at 25D can be inverted, and a service manifold 100G can direct a water from a source 116 upwardly into the cup manifold 25D. This will provide a wash at each of the cups 32, and the wash water can flow out into a waste receptacle 266, for draining or capture. The frame 250D for supporting the service manifold 100F can be fixed into position, or can be movable up to seal the service manifold 100F against the edges of the cup manifold 25D, if desired.

In a station 248E, a second wash can be provided, in the same manner as the first wash using a

service manifold 100G to provide a second wash from water source 116. A second waste receptacle 266 can be used for providing water that drains out, or if desired, again, the service manifold 100G can be raised  
5 to seal against the cup manifold 25E if desired.

At the next station 248F a cup manifold 25F is provided with a rinse from a service manifold 100H, providing water from a source 116. Again, a waste receptacle 266 can be provided for catching the water  
10 that is draining out, and sending it to drain.

At the station 248G, a cup manifold 25G is supported above a service manifold 100I to provide dry gas on the interior of the cup manifold 25G from the gas source 140. This service manifold 100I also can be  
15 fixedly mounted, so that the dry gas merely blows up into the interior of the cup manifold 25G. After indexing again, to a station 248H, the cup manifold 25H is positioned upright, and a service manifold 100J can be used for providing a coating material from a coating  
20 source 142. The service manifold 100J may be mounted on a vertically moveable frame 250H to seal on the cup manifold 25H, if desired, as well.

Then, after the coating has taken place at each of the cups 32, in the cup manifold 25H, the  
25 process will start again for the cup manifold by indexing to the station 248A where the dosage device 17 would provide a metered dose from an inhaler into the underlying cups in the cup manifold 25A.

It should be noted that the cover and seal plate or impactor assembly 21, when it is removed for cleaning, can be removed with a robot arm such as that shown for operating and moving the preseparator and the induction port 14 as shown in Figure 22, or it can be made in a cartridge type arrangement where they can be interchanged when needed for cleaning.

In Figure 28, a schematic showing of another form of injector used for injecting solvents from a reservoir simultaneously, or substantially simultaneously, into the individual cups of a cup manifold is illustrated schematically. A solvent reservoir indicated at 300 connected with eight lines indicated generally at 302, to individual valves 304, 306 and 308. The valves 304 and 306 are triple valves that are three-way valves that will permit rotating and connecting three different lines to inputs or outputs as desired. A double three way valve for two inputs is shown in the valve 308.

Each of these valves has a port connected to one of a plurality of syringe solvent injectors 310A-310H. As can be seen, the injectors 310A-310F are smaller sized than the syringes 310G and 310H, and are ganged together with a bar 312, onto which an actuator 314 is connected for moving the plungers on the interior of the syringes to first intake solvent for the reservoir 300 when the valves are appropriately set to connect the lines 302 through the valves to the input ends of the syringes. The syringes 310G and 310H

have an actuator bar 316 that also is connected to the actuator 314, which is a power actuator, and will be operated substantially simultaneously with the bar 312.

There is a charge in each of the barrels of the syringes 310A-310H, as shown in Figure 28 in the present state, the actuator 314 is reversed to move the plungers toward the closed ends of the barrels of these syringes, and at the same time the valves 304, 306 and 308 are set to provide connections from the interior of each of the individual syringes to an associated output line 320A-320H. These lines in turn are connected to the individual cups 32A-32H, as illustrated schematically. The solvent can be precisely measured by movement of the syringes, and injected into the lines to the individual cups. The larger size cups that are shown, are the ones that would receive the greater amount of solvent from the syringes 310G and 310H.

The triple three and double three way valves are commercially available valves than can be operated by the controller 97 under a selected program. With the device of Figure 28, there is no need for zigzag passageways in the service manifold.

Although the present invention has been described with reference to preferred embodiments, workers skilled in the art will recognize that changes may be made in form and detail without departing from the spirit and scope of the invention.